output of uric acid is greatly altered. Experiments made with uric-acid injections prove their toxic character; the inflammation and the pains provoked by them resemble in many respects those occurring in attacks of gout.

Though conceding this, von Noorden, a number of years ago, following Ebstein's theory of the formation of uric acid in the bones, expressed the opinion that the deposits of uric acid were quite independent of the general metabolism of uric acid. Although local influences play an impotant part in gout, this view of von Noorden is easily refuted. The microscope shows clearly that the crystals are first found near the free surface of the cartilage and that they advance slowly toward the deeper layers. Thus, they must pass from the cavity of the joints into the cartilage. Secondly, when a tophus on the finger reaches the size of a chestnut, and even larger, it is impossible to imagine that the enormous masses of sodium urate stored up here could be formed in loco, even in the course of many years. The metabolism of connective tissue is much too torpid, and nuclear material, known to be the sole source of uric acid, is contained in only small amounts in the cuticle and neighboring tissues. Moreover, whenever one finds deposits of sodium urate in the body, that is, whenever gout is apparent, there at the same time an excess of this substance occurs in the blood. Although this principle is not reversible, it proves certain connections between the local and the circulating uric acid.

PRELIMINARY NOTES. In reference to uric acid, gentlemen, please remember that in reality we have to deal only with monosodium urate in the fluids within the body. Some authors have assumed the existence of a quadriurate of sodium, or, as we would call it now, of monosodium biurate or hemiurate; others have insisted that in a fluid containing a number of basic molecules like serum, the chemical union of an acid with one of the bases could not be recognized. Physically considered, there exists no monosodium urate in the serum, no more than monosodium carbonate. All these salts are dissociated into their ions, and we have to deal only with sodium, potassium, calcium ions and with uric, chloric, carbonic acid ions, existing side by side. But with the same right with which one speaks in the common language of chemistry of the existence of sodium chloride, of monosodium carbonate, and monosodium phosphate in the serum, with just as much right one may also speak of monosodium urate. Ninety per cent. of the kations in the serum belong to the sodium, only 10 per cent. to potassium, calcium, and so on. In a neutral solution which, in a physicochemical sense, the serum is, the proportion between kations and anions, or between acids and bases, is such that we can only speak of monosodium carbonate and of monosodium urate. The existence of bisodium urate is just as impossible here as the existence of bisodium carbonate. It is to Gudzent that we owe the clear exposition of this.

FUNDAMENTAL PRINCIPLES. As compared with former times, we now stand on a firm foundation in regard to our knowledge of the formation of uric acid. This substance is derived from the nuclear purins, adenin, guanin, hypoxanthin, and xanthin. Their transformation into uric acid is the work of hydrolytic, of desamidizing and oxidyzing ferments. The ferment which katabolizes uric acid is called the uricolytic ferment. I need not detail these processes, but will refer you to Prof. Mendel's lecture delivered on this subject three years ago before this Harvey Society.

This being established, two questions arise:

1. Whether this intermediate path of metabolism is obligatory in the sense that every molecule of the purin bases must reach the stage of uric acid, or whether adenin or hypoxanthin, and so on can be katabolized without first being converted into uric acid. Thus far the possibility of the latter proposition has never been demonstrated in the organism. Chemical considerations and biological analogies lead us to consider the transformation of purin bases into uric acid as the only process effective in mammals.

2. The second question, whether in mammals there are still other sources of uric acid, is doubtful. No proofs have yet been brought forward of a formation of uric acid from urea and from acids with three-carbon atoms, a process which is of fundamental importance in birds. So we may neglect this kind of synthesis. On the other hand, it is beyond question that purins are newly formed in suckling animals whose food is practically purin-free. It seems improbable that the synthesis effected here starts from urea; we must rather look for a higher amino-acid compound, as a material which can yield purins. It would be very surprising if this synthesis were performed on a larger scale than was needed for the growth and for the renewal of the tissues, that is, for the synthesis of nucleoprotein. I do not think that in this process an excessive formation of purins takes place, or that superfluous material for the formation of uric acid is left over. We may with our present knowledge consider the purins as the only source of uric acid in human metabolism.

We distinguish the exogenous purins ingested with the food from the endogenous derived from the nucleins of the body. By dieting we can make ourselves independent of the great variations in the output of uric acid due to the different amounts of ingested purins. By giving a purin-free food, which need not be absolutely the same every day, the urine will contain endogenous uric acid only. The quantity eliminated, although varying in different men from 0.3 to 0.6 gram, is fairly constant in the same person under normal conditions, thus proving the existence of an equilibrium between the formation and the destruction of uric acid. The simplest conception of this is, not that formation and destruction vary always in the same sense and proportion, but that both formation and oxidation are constant.

The katabolism of uric acid leads to the formation of allantoin in dogs and rabbits. In man its fate is unknown. In contrast with the results in most animals, human organs have failed to show a distinct uricolytic power. Hence Wiechowsky drew the conclusion that uric acid was indestructible in the human body. He based this opinion also on a second fact, namely, that uric acid injected into the muscles of men is found again almost quantitatively in the urine. Schittenhelm although confirming Wiechowsky's experiments with human *organs*, was able to show that uric acid undergoes destruction in *living* men. When a person, who was in nearly perfect nitrogen equilibrium, was fed with 10 grams of nucleic acid, the output of purin substances was only slightly increased, and instead, an increase of urea (or a substance behaving similarly) was found, and in amount corresponding nearly to that of the nitrogen of the ingested purin compounds. It would be of greatest interest for physiological chemistry to determine what are the intermediate and end-products of the uric acid breakdown; but for the knowledge of gout, this is of less importance. It suffices for the present to know that this toxic substance disappears as such.

If Wiechowsky's opinion were right it would mean a simplification of experiments and of theory, for one unknown component in the complex equation of urate metabolism, the destruction of uric acid, would be eliminated. Recapitulating, one may say that the present foundation for investigations of the metabolism in gout is as follows: We have to deal only with *one* source of uric acid, namely, the purins; and, after excluding the exogenous purins, we find a uniform elimination at certain periods. This we accept as a firm basis for comparison, both as regards the metabolism of healthy men and also with regard to the variations which occur in different periods of gout.

THE FACTS IN GOUT. What are the facts in gout which are established with such accuracy that we can take them as a basis for our consideration? What results are sufficiently probable to be taken into serious discussion? The facts and the probable truths are as follows:

1. The presence of uric acid in the blood.
2. The presence of crystalline deposits.
3. The increased output of uric acid in the attacks of gout. The augmentation can reach from 0.3 to 0.5 gram daily and more, and may sometimes last for a week or even two.
4. A decline in the output of uric acid often precedes the attack of gout, but this diminution is not as marked as the subsequent increase, and its duration is only one or two days.
5. In the intervals between the attacks of gout the elimination of endogenous uric acid is asserted to be lower than in health.

There are doubts whether this statement has been proved beyond question.

6. The elimination of exogenous uric acid is often retarded.

To elucidate the connections between these data it would be necessary to have a complete knowledge on the quantitative side of the following processes in both health and disease:

1. Of the formation of uric acid.
2. Of its destruction.
3. Of its elimination by the kidneys.

From a combination of these three processes would arise a knowledge—

4. Of the accumulation of urates in the body, especially in the blood.

5. We ought to know the conditions of the sodium urate precipitation in the tissues, as well as the conditions for its removal. Herein is included a knowledge of the physical and chemical behavior of sodium urate.

THE FORMATION OF URIC ACID. Is the formation of uric acid increased or is it diminished in gout? In almost every case in which we see an increased output of uric acid, for example, in leukemia and pneumonia, we find an increased destruction of nuclear material, and vice versa. In gout, at least in the intervals and when the patient is given purin-free diet, neither one nor the other is to be observed. The katabolism of nuclear material therefore is certainly not increased.

On the other hand, we have just as little reason to assume a diminished formation. Brugsch and Schittenhelm, it is true, have recently advanced the theory that the total nuclear metabolism in gout is retarded. But even if this were true, I must insist that retardation of metabolism is not in every case identical with diminution. Perhaps in *advanced* stages of the disease, a decrease in the formation of nuclear compounds may take place, due to a kind of cachexia of premature aging. In the experiments made hitherto I miss a clear distinction and separation as to the age and the general state of health. Most of the gouty patients treated in hospitals are in an advanced stage of their illness, and evince signs of cachexia, even when showing a good volume of muscles and of subcutaneous fat. The healthy people, whose nuclein metabolism has been compared with that of the gouty, were generally younger. In order to obtain a more reliable material for the comparison between normal and gouty metabolism, stricter attention ought to be paid to this point regarding age. Bearing this criticism in mind, the following exposition may be considered. In any case it seems to be certain that, in opposition to former opinion, the occurrences in gout cannot be explained by excessive formation of uric acid. In the older days whenever an increased output of uric acid was noticed the cases were mostly those of wealthy people overfed with meat. Gouty patients are generally hearty eaters. The high amount of uric acid in these people is due to the ingested purins, not to the diathesis. Analogy with obesity produced by polyphagy is striking. The gouty process, though no doubt aggravated by an excess of exogenous purins, does not depend on an increased uric-acid formation.

THE DESTRUCTION OF URIC ACID. In many experiments the twenty-four hour output of uric acid in the urine of gouty men is diminished. So far as this is not due to lessened formation, it proves an increase in the *absolute* quantity of uric acid destroyed. The accumulation in the body does not reach such an extent as to explain the difference of excretion between healthy and gouty men. This difference often reaches 100 mg. in 24 hours. Supposing this quantity were retained in the body day by day for one year only, the total sum would amount to 36 grams. Deposits of such enormous size are extremely rare, at least in Germany. I doubt whether in the majority of cases 10 grams of sodium urate may be extracted from the gouty body. Since the lower quantity of uric acid in the urine is not explained by an accumulation, it must be ascribed to increased destruction. As Brugsch and Schittenhelm rightly suggest, this does not mean absolutely that the oxidizing power of uricolytic ferment is greater than normally or that its quantity is increased. The reason may be that each molecule of uric acid circulates a longer time in the body; thus it is exposed more often to the influence of the oxidizing ferments, and thus there is more chance for its destruction. The investigation of the blood renders it probable that such prolonged circulation of urates really occurs in gout.

The conclusion that the *endogenous* uric acid is katabolized in greater amount is confirmed by the results of experiments in which the fate of *exogenous* purin was studied. In a great number of these observations the output of uric acid after feeding sweetbread, or other nuclein-containing material, was less than in healthy persons. It also is to be remarked here that more time is needed for the elimination of exogenous purins than normally, in spite of the fact that smaller quantities are excreted. Different gouty patients do not behave alike. There are some in whom destruction and elimination are performed in the same length of time and to the same extent as in healthy persons. It would be premature to assume a retardation of the purin metabolism as being the constant rule. I refer again to the above-mentioned objections concerning the influence of age and general state of health upon the purin metabolism.

THE EXCRETION OF URIC ACID. The excretion of uric acid by the kidneys depends, like that of any other substance, on two factors. The elimination can be diminished when the secretory power of the kidney is lessened; and it can be prevented also when the substance in question is united to another complex and thus bound.

In nephritis elimination of uric acid is markedly disturbed. Thus, during favorable periods, even when no other substance is retained (in any amount worth mentioning), some milligrams of uric acid are always present in the blood of the nephritic patient. It seems to me as though the special capacity for the excretion of urates is more limited and can more easily become deficient, than any other function of this organ. I will try to explain this.

In administering an excess of any substance, the level of its end-products rises in the blood. This is due to the fact that the output by the kidney does not keep pace with the influx into the blood. But though with every other substance the level rises only by a small amount, with *uric acid* it may rise to ten times its normal height. While scarcely ½ milligram is contained in 100 c.c. of normal blood, Weintraud found 5 milligrams after feeding with an excess of sweetbreads.

I may now speak of the second factor, that is, the preventing of the elimination of a substance by its chemical combination with another. Such a theory has been offered in order to explain the non-excretion of sugar in the healthy organism. Minkowski tried to introduce this idea into the theory of gout. He assumed a chemical union of uric acid with a nucleic acid. But the search for such a compound in the blood has not been successful. Gudzent, on applying Michaelis' method of compensation to the dialysis of gouty blood, was able to show that the urates exist only in the free state. I might also mention Garrod's thread experiment as speaking against any organic union. Acetic acid, which sets free all uric acid in the serum, or at least the greatest part, is an extremely weak acid, its strength being some hundred times less than that of hydrochloric acid. Under the conditions of the thread experiment it would not suffice to split any organic union.

The hypothesis of Minkowski having been thus refuted, Gudzent showed another possibility. By physico-chemical methods he pointed out that the sodium urate exists in two modifications, which differ only in their solubility. He ascribes the existence of these two forms to a difference in the chemical structure, to a tautomerism. The lactam form, that is the substance having the formula which is generally used for the structure of uric acid, is the more soluble one, but tends to pass into the lactim form, which is less soluble. If the difference in solubility of the sodium urates is really due to a difference in the chemical structure, and not purely to physical reasons, one could imagine that the tautomeric forms would behave differently in regard to their excretion by the kidneys. Experiments in this direction have not been performed.

URIC ACID IN THE BLOOD. Normal blood is practically free from uric acid. In gout it can contain 5 to 10 mg. per 100 c.c. after a mixed diet has been taken; following a purin-free diet the amount is lower, being from 2 to 4 mg., but in no case is uric acid absent. Its presence in gout cannot be explained by an excessive production of uric acid, as is the case in leukemia and in pneumonia. This conclusion, though it is contrary to the opinions of a former time, is beyond doubt.

It can be attributed chiefly or partly to a passive retention in those cases in which the kidneys are suffering, either from the beginning —what has been called kidney gout (Nierengicht)—or in later stages of the disease. On this point no controversy exists between the different authors. But how is the presence of uric acid to be explained in those cases in which the most accurate research does not reveal any sign of nephritis? The answer is only to be given conditionally.

If neither the formation of uric acid is increased, nor its destruction greatly diminished—and these two conditions seem to be realized in gout—if, moreover, the uric acid is not prevented by a chemical union or by an abnormal structure from passing into the urine, only one conclusion is possible. The retention is due to a deficient and restricted secretory power of the kidneys.

The existence of such a renal inadequacy does not mean a real nephritis. I think it possible that a single function of this organ can become almost exclusively insufficient. Later on, real damage to the kidney and a nephritis frequently follow.

As stated already by Garrod, uric acid is present also in lead poisoning. Here, as in gout, it is present at a time when no sign of nephritis can be noticed. Concerning this phenomenon, resembling that in gout, one may assume the same explanation, namely, a deficiency in the secretory power of the kidneys, or a kind of incipient and latent nephritis.

If one is not willing to accept the above explanation for the very early stages of gout, because of the absence of albuminuria, he must deny it also for the first periods of lead poisoning. Whatever interpretation avails in gout must also be admitted for lead intoxication. *In any case the mechanism of the accumulation of urates in the gouty blood is not a specific phenomenon of gout.*

Brugsch opposes this explanation on account of an experiment in which uric acid injected into the muscles of a gouty patient was eliminated just as completely and quickly as in a healthy man. I do not consider this objection to be conclusive. The gouty kidney, although not able to eliminate one gram of urates quickly enough on the *normal* level of urates in blood, might accomplish this task very well at the higher level already existing before the injection of uric acid. That this conception is right Widal has obviously proved by the example of the behavior of urea in nephritis.

Brugsch and Schittenhelm fall to a somewhat mystical explanation. They ascribe the accumulation of urates in the blood to a diminished destruction. But when a substance has once entered the blood, its elimination depends *only* on the relation between this fluid and the kidneys. I think the following argument will be convincing. On feeding sweetbreads, or during the absorption of pneumonic exudates, the blood contains just as large a quantity of urates as does that of a gouty patient. Now, persons who do not suffer from gout will eliminate the excess of urates within a few days, and, even when adhering to a mixed diet, their blood will soon be free from urates. In gout, on the contrary, notwithstanding the ingestion of a purin-free diet, under the influence of which the formation and the influx of uric acid into the blood is much lower, uric acid will by no means disappear from the blood. Brugsch and Schittenhelm ascribe this to a retarded decomposition, though conceding that the total amount of uric acid breakdown is above the normal. Something is lacking in their theory, and they seem themselves to be aware of it. Although denying that the threshold (Schwellenwert) of the kidney for the output of urates is elevated in gout, they speak of a certain torpidity of this organ.

The deduction which ascribes the retention of uric acid to a damaged function of the kidneys, as enunciated by Garrod and adopted since by several authors, is rather repugnant to me as well as to pathologists in general. The disturbance which affects the entire organism would, according to this opinion, depend principally on the *passive* retention of a single metabolic product. This conception is not very satisfactory. I would be very pleased, indeed, if any other solution of the problem could be found. However, *rebus sic stantibus*, and without fixing my opinion for the future, I find no other solution for the problem than that given above.

This interpretation might terminate the unpleasant dualism in the theory of gout. The distinction between a primary metabolic and a primary kidney gout, which has always found supporters, from Garrod down to Brugsch and Schittenhelm, would become unnecessary by adopting this interpretation.

But against the doctrine of gout being due to deficient kidney functions, clinical doubts arise which we are unable entirely to remove. Why does not gout appear in each case of nephritis, why not in leukemia in which we always find an excess of uric acid in the blood? Many cases of interstitial nephritis progress so slowly that secondary changes, such as the deposition of urates and other abnormal phenomena, might have time to develop. Is perhaps the retention of uric acid present only in the later stages of contracting kidneys? We know nothing certain about this, nor about the supposed deficiency of the kidneys in gout. Does the condition reach back to youth, or even to childhood? The deficiency in that case would have lasted much longer than in any case of nephritis. At any rate, we must emphasize the fact that in many autopsies on uremic subjects concretions are found in the joints, without any history that the patients had ever suffered from primary gout. There is no doubt that organs other than the kidneys must play an important part in the pathogenesis of gout.

Of all the tissues, only the *joints* and the part they play in the pathology of gout can be discussed in detail. Are the cartilages and the connective tissues implicated only in a passive way in gout, or are they active? Further questions to be answered are the following: By what mechanism and at what period does the deposition occur? What symptoms are produced by the precipitation of crystals, and what happens to the crystals during the paroxysm?

Contrary to the opinion of Ebstein, we may at present take for granted that the deposition of urates does not occur in necrotic, but only in living tissue (Minkowski, Freudweiler). And also in these deposition can only occur if the liquids which circulate in them are saturated with sodium urate. As to this point, whether the amount of urate of sodium in the blood corresponds to the saturation point, the opinions of most authors are or were erroneous. It was generally believed that the serum of the gouty patient is not saturated with urate of sodium. This assumption has been put forward on account of the experiments of G. Klemperer. He observed that 100 c.c. of normal serum can dissolve 150 to 200 mg. of uric acid, that is, ten times more than it ever contains during life. The serum of a gouty patient behaved in the same manner. This observation is correct—of that there is no question. But Klemperer failed to observe the reaction to its end; if he had done so, he would have seen after some time the abundant precipitation of urates. Serum, indeed, has the power of dissolving a good deal of uric acid by transforming it into urate of sodium, but only a small amount of the sodium salt is kept in solution. The problem has been attacked from a wrong direction. The biological question is not how much uric acid can be transformed by the alkalies of serum into urate of sodium, but how much sodium urate the serum is able to take up without precipitation. Roberts, in 1890, carried out experiments, and by the use of a correct method found that serum holds only a few milligrams of urate of sodium in solution. The figures found by Gudzent twenty years later were almost identical with those of Roberts, and with those Gudzent had in advance calculated theoretically that 100 grams of serum is saturated when containing 8 mg. of urate of sodium. If we apply these figures to the free acid instead of to urate of sodium, and to blood instead of to serum, we are surprised to see that 100 grams of blood is saturated when it contains 4 milligrams of uric acid. Such an amount has, indeed, been found in the blood of people suffering from severe gout, when on a mixed diet.

As to the point of saturation the conditions for precipitation are nearly always present. In the circulating blood, however, precipitation never takes place; it is prevented by its continuous movement and by the perpetual exchange of the urate molecules. While some of them pass to the urine, others enter the blood from the organs.

THE PRECIPITATION OF URATE OF SODIUM. The conditions for precipitation are much more favorable within the lymphatics and within the synovia of the articular cavities than elsewhere, for here the flow of liquids is very slow. I myself found 4 and 6 milligrams of uric acid in 100 c.c. of the fluid aspirated from inflamed knee-joints. But in spite of this saturated state one rarely finds crystals in suspension, and when such are encountered they may, perhaps, have originated from the impregnated cartilages which have undergone destruction, or from tophi which have forced a way into the articular cavity. As a rule, crystallization takes place only in the organized tissue.

By many it has been taken for granted that the cartilages possess a *specific* power to attract dissolved urate of sodium and to bring it to crystallization. However, the phenomenon can also be produced by excised cartilaginous tissue. This was shown by Roberts many years ago, and later by Almagia and Brugsch. Tarsal bones of a pig were suspended in phials charged with a saturated solution of urates; after a few days they were encrusted with needles and presented an aspect which, in intensity and distribution of deposits, resembled that of a gouty joint. The process of precipitation is thus not a vital one, but is purely passive, brought on by certain chemical relations and properties still existing in the dead cartilaginous tissue. But possibly even this chemical reaction is not of a complicated order. Roberts, in a purely experimental way, showed that the solubility of sodium urate decreases with increasing concentration of sodium salts in the liquid. The theory of solution agrees fully with the actual experiment. An addition of 0.2 per cent. of sodium chloride to a saturated solution of urate of sodium brings about precipitation. Roberts and Gudzent noted that cartilage, tendons, etc., are richer in sodium salts than the blood serum. Their sodium content reckoned as sodium chloride rises to 0.9 per cent., while in serum it is only 0.7 per cent. When the lymph saturated with urate of sodium penetrates into the cartilaginous tissue where the concentration of the sodium ions is higher, a state of supersaturation is brought about, and precipitation can take place. In this hypothesis the supposition is made that the sodium exists in the state of ions in the cartilages. Whether this is true or not is unknown. If it does not thus exist, if it be united to an organic compound, the explanation of Roberts and Gudzent would not hold good.

In response to the question why precipitation does not occur in all joints—their chemical composition being the same everywhere—we must refer to mechanical and thermal injuries, the influence of which on the localization is clearly proved by daily experience, even though we do not find such explanations satisfactory.

But the nephritic patient is exposed to the same influences. Why does not precipitation occur in every man suffering from contracting kidneys? For the second time we are obliged to put this question. If the retention of uric acid in the blood is a passive process, if the deposition within the tissues is a purely physical process, by what properties is gout then to be characterized?

There must be an active element in its pathogenesis belonging exclusively to the gouty diathesis. What then is this active principle? Science as yet gives no answer to this question, which touches the kernel of the problem. Therefore, I will not attempt to present any hypothesis. Surely an hereditary influence exists in gout and a neuropathological influence is present besides the chemical or humoral-pathological. The clinician must always be aware of this. But so long as we cannot determine the mechanism by which the nerves act on the metabolism in gout, no scientific advantage results from, emphasizing such an influence.

All organs yielding or destroying uric acid (and they are many) were at one time thought to be implicated in the phenomena of gout. Thus, a predominant part was formerly attributed to the liver, to the bowels, or to the spleen, etc. But their influence, if indeed any exists, is not a directly controlling one over the uric acid metabolism. It is for the present worthless to search for increased or for decreased destruction in the single organs, since we know that *as a total* the uric acid metabolism always remains within the ordinary limits. If muscular work prevents paroxysms or lessens their violence this need not be referred to an increased destruction of uric acid, but rather to an immediate action on the joints, changing the quantity of synovial liquid or its composition, or the rapidity of its circulation. The action of other organs too might be indirect.

Thus the so much sought for active principle which causes gout remains a mystery, not to be unravelled by our present means. Leaving the solution of the problem to the future, we return to the fate of urate deposits. We can discuss apart this question without regard to the problems of gouty diathesis and pathogenesis.

THE RELATION BETWEEN THE ATTACKS AND THE URATE DEPOSITS. At what time does precipitation take place? Is it a chronic process going on continuously, or does it depend upon attacks and in what manner is it connected with them? When considering those tophi, the fate of which we can trace with the eye, we know that they may appear, grow, and disappear without the bearer knowing anything about it. Especially the larger deposits, those upon the hands, grow with hardly any inflammatory reaction. But this fact does not absolutely exclude a relation between the precipitating process and the attack. The same process which on slow development causes no strong reaction, may induce the most violent symptoms if the onset is one of great intensity.

According to Garrod the attack is provoked by a sudden precipitation of crystals in the tissues. The attack consists merely of such deposition of urates and of the inflammation induced by their presence. The deposits, once formed, remain for a long time, often throughout life. "When crystallization of the salt takes place in any tissue, inflammation is suddenly lit up by its presence and a paroxysm of gout ensues." Roberts is of the same opinion.

There is one objection which renders it difficult to consent in this respect to the authority of the eminent English clinician. One of the chief rules of chemistry *corpora non agunt nisi soluta* is applicable also to the conditions in the organism. If the uric acid salt is precipitated, the chemical influence of the solid material upon the tissues stops instantly and does not reappear until it is dissolved again. In the meantime its action is purely physical. The mechanical irritation may perhaps be stronger at the moment of crystallization and during the growth of the crystals than in periods of absolute rest. But the pressure which the crystals exert upon the tissues is scarcely sufficient to bring about a serious reaction. Garrod's opinion is just as improbable to me as the hypothesis which refers the symptoms of bronchial asthma to an irritation of the air conduits by Charcot-Leyden crystals. In opposition to the English authors, I am rather inclined to ascribe the irritation to the dissolved urates. According to this conception a sudden increase of their concentration would induce the inflammation.

This supposed rise of the amount of urates within the synovia could be brought about in a twofold manner. According to Garrod's opinion it is only a part of the general urate accumulation in the whole body, induced by a deficient excretion. The urate molecules would pass from the serum to the synovia and thence to the cartilages. However, a contrary conception could also be supported. A rapid solution of the deposits might lead to an increased concentration in the synovial liquid, thus perhaps explaining the violence of reaction better than the hypothesis of Garrod. As to the question why a solution of deposits should occur so rapidly, I own I am not able to reply.

The above conception is an elaboration of Pfeiffer's ideas somewhat changed. In opposition to Garrod, Pfeiffer considered the attack as consisting of a solution and removal of the deposits of urate. He based his opinion upon reasons which do not seem to me to be justifiable. Still his idea as a whole seems to me probable, and for the two following reasons:

1. The inflammation spreads far beyond the places of the crystalline deposits. One may find an aspect of the skin fully resembling a phlegmon, and even a severe lymphangitis, which, though aseptic, has sometimes misled the surgeon. This proves that an irritating substance is carried away from the afflicted joints. If the sodium urate is really the inflammatory agent in the joints, it seems likely that the irritation of the more distant tissues is caused by the same substance, carried away through the lymphatics.

2. The second reason in favor of Pfeiffer's views is the excess of endogenous uric acid excreted during the attack. The excess is far greater than the diminution preceding the paroxysm. In one

of my observations the surplus eliminated in eight days of a violent attack amounted to more than 3 grams. Although the origin of these urates cannot be pointed out with accuracy, it may probably be attributed, in whole or in part, to a solution of the crystalline deposits.

I might also lay stress upon the fact that, in aspirating the joint exudate as completely as possible, the last portions, originating from the interior parts of the cavity, are always found to be richer in leukocytes than the first portions. And it is well known, that leukocytes are the instruments for attacking the urate crystals as well as the vehicles for their removal. Perhaps the theory of Garrod and that of Pfeiffer might be combined in such a way as to assume that a general retention of urates provokes the outbreak of an attack, and that the inflammation which follows leads to a removal of the deposits.

PECULIAR EXCITING CAUSES OF THE ATTACKS. The accumulation of uric acid in the fluids of the body, supposed by Garrod to precede and to provoke the attack, has not yet been demonstrated by analysis of the blood itself. If it were possible to determine the uric acid in the blood day by day before and during the paroxysm, we would be able to judge the part played by the accumulation of urates better than we can now. We are at present obliged to rely upon analysis of the urine. The decrease of the uric acid output in the twenty-four hours prior to the attack, which amounts to from 100 to 200 mg., may be interpreted as meaning an accumulation in the body; but sometimes this decrease is altogether lacking. The best support of this part of Garrod's theory is to be found in the more recent observations that consumption of sweetbread *sometimes* brings about the paroxysm. It may be asked whether this coincidence is not merely accidental. In spite of such doubts and gaps, this part of Garrod's doctrine is generally acknowledged and accepted.

However, this is not true with regard to the second part of his theory. Garrod assumed a decreased alkalinity of the blood to be the second cause exciting the gouty attack. *This part of his doctrine should be dropped entirely.* It is refuted by actual examination of the gouty blood as well as by proofs in the test-tube, and it is contradicted also by the doctrine of physical chemistry. In measuring the alkalinity of the blood by means of titration in more than twelve patients before, during, and after the paroxysm, and also during the intervals, I failed at any time to find any marked difference. Moreover, all chemical analogies teach us that an addition of hydrochloric acid to the solution of any salt may bring about precipitation of the *free* acid, but never that of the *salt*. If we had to deal with bisodium urate, the addition of an acid would produce its conversion into monosodium urate, and this, being less soluble than the original salt, would crystallize out. This would be the same process as the precipitation of monosodium sulphate produced by adding sulphuric acid to a solution of neutral sodium sulphate. But please remember, gentlemen, that in the serum only monosodium urate is present, which, according to the above exposition, is not precipitated as such by acids.

Roberts' test-tube experiments correspond fully with these theoretical deductions. Serum contains about 0.5 per cent. of sodium chloride and 0.2 per cent. of monosodium carbonate. The addition of hydrochloric or acetic acid to serum saturated with urate of sodium brings about a precipitation of uric acid. If, on the other hand, sodium carbonate be removed from the serum by dialysis, not the slightest crystallization occurs, although the serum has lost its alkalinity. On the other hand, the addition of monosodium carbonate to the serum causes precipitation, although this be contrary to Garrod's opinion, and in spite of the high increase of the so-called alkalinity. The solubility and the precipitation of urate of sodium have nothing at all to do with the alkalinity, but depend merely on the concentration of sodium ions or salts in the solution. Indeed, the addition of sodium chloride effects a precipitation just as well as does monosodium carbonate.

The question of diminishing alkalinity is of the utmost importance for the precipitation of uric *acid* in urine; it is predominant in the pathogenesis of *gravel*, but it must be excluded entirely from the theory of gout. It has to be replaced by the factor of salt concentration, and especially of the concentration in sodium ions. Please remember, gentlemen, in connection with these explanations, the conception of Roberts that it is the high amount of sodium salts in the connective tissue which very likely determines the place of the crystallization of urates.

It will be hard for many to drop entirely the doctrine of the importance of a varying alkalinity of the blood in gout. One may feel inclined, perhaps, to found his conservatism on the valuable experiments of Loghem. This Dutch scientist has found that deposits of uric acid, produced by hypodermic injections in the rabbit, are soon converted into deposits of urate of sodium, and that this transformation is followed by a serious inflammation. In dogs this transformation is not observed, nor any inflammation. The metabolism of the rabbit kept on green food is, roughly speaking, an alkaline one. In the same sense, we might apply the term of an acid metabolism to a dog fed with meat. According to this difference the fate of uric acid injected varies in the two species. But if the dog has been given 20 grams of sodium carbonate, his metabolism becomes more alkaline, and the conversion of the uric acid into urate of sodium takes place exactly as in the rabbit. Vice versa, in the rabbit it is prevented by administering hydrochloric acid. The results of the older experiments of Pfeiffer and the later ones of Silbergleit coincide fully with those of Loghem.

In these experiments the influence of acids and alkalies upon the chemical occurrences in the body are evident. In many respects these experiments are of high value, and have justly attracted attention. However, the observations have nothing to do with the conditions in gout. In Loghem's experiments an entirely different problem was attacked, namely, the transformation of uric acid into urate of sodium. It is obvious that the transformation is favored by an excess of alkalies in the body, as well as in the test-tube, and that it is retarded or prevented by an increase of acid substances alike in the body and in the chemist's phial. As to the solubility and precipitation of urate of sodium, Loghem's experiments prove just as little as Klemperer's experiments about the degree of saturation of serum with urate of sodium.

THERAPEUTICS. If I now consider the therapeutics of gout, I must of course confine myself to the discussion of such points as bear relation to the metabolism of uric acid.

The two drugs which are the most efficacious in the paroxysm, colchicum and salicylate, behave entirely differently as regards the elimination of uric acid. Salicylates in sufficient doses increase the output of uric acid materially, by half a gram and more daily. This effect, however, seems to disappear within a few days. Colchicum, which, no doubt, is the stronger remedy, produces no change, or, if so, it diminishes the quantity of uric acid elimination. I do not believe that these two drugs, the chemical effects of which are so different, owe their efficacy to the same pharmacological action. One should try to define the mechanism of their action. Setting aside their soothing capacity, I shall only discuss their action upon the uric acid within the body.

If, according to Pfeiffer's opinion, the attack were a process of solution and removal of urates, one could conceive that salicylates favor the elimination, since increased uric acid output follows the administration of these substances. But we do not know whether this increased output originates from the deposits. Even healthy persons when taking salicylates show a slight increase of uric acid elimination. Comparative experiments with this remedy ought to be made on a large scale upon healthy and gouty people.

As to colchicum, one might think that it inhibits the process of solution, thus putting an end to the inflammation and to the paroxysm. Its effect is certainly more rapid and more intense than that of sodium salicylate. If this conception were right the colchicum would be only a palliative for the attack, while the salicylates, in spite of their slower action, would be the preferable remedy. It is well known that colchicum is useless in chronic gout. If the attack be interpreted in the sense of Garrod, the efficacy of both drugs would have to be explained otherwise. A discussion of this subject bears as yet the character of mere conjecture. Therefore, I do not wish to enter into details. I have felt that the ideas were worth mentioning in order to encourage investigations on these points.

Alkalies and acids are not given during the attack, at least not in large quantities. However, considering the importance of these substances in chronic gout, their application should be tried and observed during the paroxysm also. In recommending them I do not expect any therapeutic effect. Indeed, in one of my patients the largest doses of hydrochloric acid did not influence either the pains or the inflammation, which is contrary to the results observed in the experiments of Loghem. In administering alkaline carbonates during the attack, I do not expect a curative effect either. I merely think that the comparative investigation of the action of acids and of alkalies during the attack should also throw some light upon their action in the chronic stages.

In the therapeutics of chronic gout, restriction of meat in the diet has been in use since olden times. This treatment is older than our recent knowledge of uric-acid metabolism. In lessening the formation of exogenous uric acid, we only practise today what the old physicians practised with less precise ideas. However, the extremists of today do not even go so far as to forbid meat entirely. Empiricism shows that the disadvantages induced by an exclusive lacto-vegetarian diet prevail over the benefits which could be expected from a diminished formation of uric acid. Generally we prescribe a diet poor in purins. Investigations of the purin metabolism during years of strict adherence to such a diet will teach us to indicate its application with more accuracy. Repeated analyses of the purin compounds in the blood are needed as well as balances of the purin intake and output, and also repeated investigations of the behavior of ingested nucleic acids. Hospital patients are not very well fitted for such researches which have to be extended for years. It is fortunate that wealthy patients of today are inclined to enter the clinics and sanatoria, and willingly to undergo longer observation. They have an appreciation of the importance of such investigations. However, it will take a decade at least before sufficient data concerning the behavior of uric acid in the urine, blood, etc., collected from a sufficient number of patients, will be at our disposal. We can look forward to this time with great hope.

Of all remedies deemed useful in chronic gout, alkalies have for centuries been applied more than all others. Two theories as to their value have existed. Regarding the first, it was believed that alkalies dissolve the concretions of urates within the body. I have already explained to you that this idea has been entirely refuted by modern research. The second quality ascribed to the alkalies was their power of facilitating the output of uric acid. This surely should be of benefit. But experiments carried out in this direction do not speak at all in favor of the conception. In therapeutics, however, the first principle for the practitioner as well as for the scientific observer is to observe and to judge therapeutic effects with impartiality, leaving aside both prejudice and theory. If empiricism should speak in favor of the alkalies, another theory is required, without need of change in therapeutic treatment.

Cool judgment, however, is more difficult in the therapeutics of gout than in any other disease. There is a lack of a pronounced criterion by which we may measure the effects of our prescriptions. In diabetes we measure the amount of sugar eliminated, in obesity the changes of weight. In nephritis, and in cirrhosis of the liver, and in diseases of the circulation, the increase or decrease of effusions and the height of the blood pressure represent the criteria of therapeutics. Even in tuberculosis and in syphillis, the course of which is so difficult to judge, there are still better points of support for judgment than in chronic gout. As yet we are allowed to judge the results of therapeutic action only by the measure of diminished urate of sodium excretion in the urine. Probably a diminished amount of urates in the blood represents a standard of improvement, but as yet this criterion is not available, and for obvious reasons. Thus, the measure by which we may now judge of lasting improvement consists merely in a postponement of the attacks, in a lessened intensity of the paroxysm, and in a diminution of chronic troubles. Regarding this point I can only repeat Roberts' words: "The incidence of diathesis even in fairly typical cases exhibits a waviness, an afflux and reflux, which is very puzzling. In the less typical cases the irregularity is such as to baffle all explanation. In most instances the manifestations become intensified with advancing years, but sometimes the converse is observed. All these perplexing vagaries are within the compass of the natual history of the disorder."

Even if a physician may dare ascribe the improvement of a gouty patient's health not to nature itself, but to his own prescriptions, to which of them is he allowed to attribute this success?

All procedures which we believe to be beneficial in gout, namely, the restriction of meat diet, the choice of green food, muscular exercise, the use of baths, all these prescriptions are generally given at the same time and accompanied by the administration of drugs; and even these the most conservative physician and patient will change time and again. Similar objections are to be borne in mind in judging the effect of alkalies. Roberts, in whom scientific criticism was united with the abilities of a born physician, asserts that in a long experience he had never seen any distinct improvement even after administering alkalies for many years.

What remedy can be substituted for alkalies? You all know, gentlemen, that a German practitioner, Falkenstein, has pleaded for the entire abolition of alkaline treatment and recommended instead the administration of hydrochloric acid. His ideas of gout and of its therapeutics stand on a very weak foundation. However, success is the decisive factor. Falkenstein reports that after years of severe trouble he finally got rid of his pains by the use of hydrochloric acid, without having changed his mode of living, his diet, or his habits. Such a report deserves every attention, even though this new therapeutic method might not benefit every patient. Falkenstein asserts that he has obtained good results in many patients. Other physicians have been less successful. Thus, we must leave time for further observations.

I wish to add a few more words regarding the use of mineral springs. Physicians are inclined at present to ascribe the undoubted efficiency of mineral waters not to the content of salts, but to the emanations of radio-active substances. Gudzent has observed that radio-emanation was able to destroy uric acid. It has been hoped that such influence is also active in the organism of gouty patients. Since the emanation leaves the body rapidly with the expired air, Löwenthal constructed a respiration chamber, in which the amount of emanation was kept at a high level. Thus, the quantity of radio-emanation from men rose to 150,000 units. Preliminary experiments were carried out last winter by Löwenthal and Gudzent in the clinic of Prof. His. The results have not been published in detail, so judgment is somewhat difficult. In healthy persons the output of uric acid was materially increased, but gouty patients behaved differently. There was a marked improvement of health, but it was not possible to refer this to a distinct change in the uric acid metabolism. In experiments with animals, however, the influence of radio-emanation was more conspicuous. The symptoms of inflammation produced by hypodermic injections of uric acid in the rabbit were modified under the influence of the emanations; leukocytosis and phagocytosis were retarded for several days. By this observation the marked influence of radio-emanation on the occurrences within the organism is established beyond every doubt. It may be hoped that investigations of this kind will advance our knowledge of theory as well as of therapeutics. Thanks to Löwenthal's ingenious apparatus, it will soon be possible for any hospital to avail itself of these new resources.

Since the production and destruction of uric acid, like that of other chemical substances, are the work of protoplasm, it is for future research to study the lesions in the protoplasm itself, and to reveal the mechanism which leads to a derangement of the metabolism. At present we only recognize the results and the chemical products of this derangement. In gout also the researches must rise from the present level to investigations of a higher order. But this is the same in every field of pathological metabolism. When, on looking back after a lapse of twenty future years, we shall have advanced into a more profound region of knowledge, we shall not regard the older investigations on uric acid as having been done in vain.

THE ELECTROCARDIOGRAM IN CLINICAL MEDICINE.

II. THE ELECTROCARDIOGRAM IN SOME FAMILIAR DISEASES OF THE HEART.

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In the preceding section of this communication[1] we have seen that the electrocardiogram in health is a curve whose general character. though subject to individual variations, is much the same in all normal persons. As might be expected, this curve is subject to very marked alteration in various diseases of the heart, and for the practical physician it becomes a matter of great interest to know what information, expressed in terms of anatomical change or alteration of function, can be derived from the study of the pathological electrocardiogram.

In considering the factors which bring about change in the form of the electrical curve, it must be constantly borne in mind that this curve is purely the expression of changes in the electrical condition of the heart, due to muscular activity. Movements of the blood or mechanical disturbances of valves have no direct effect on this record.

It has been previously shown that the character of the curve varies with the points of the body surface from which the current is led off. A theoretical consideration of the physical laws which determine the spread of potential would carry us too far afield. It may be stated as an observed fact that variations in the position of the heart within the chest will also cause marked changes in the form of the electrocardiogram.[2] Similarly, marked changes in the shape of the muscle mass affect the curve. Still more striking variations are those caused by contractions which originate in abnormal situations and pursue an abnormal course through the muscle.

We shall present records of some of the more common of these conditions with such comment on their interpretation and significance as seems desirable from the standpoint of the practitioner of medicine.

Hypertrophy. Our knowledge of this subject is at present largely empirical, and analysis of the exact conditions which bring about the observed changes is beset with very considerable difficulties. Further study may eventually permit such an analysis, but for the present we shall confine ourselves to a description of the form of the curves with which we find hypertrophies associated.

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[1] Amer. Jour. Med. Sci., 1910, cxl, 408.

[2] Einthoven, Weiteres über das Elektrokardiogramm, Pflüger's Archiv, 1908, cxxii, 533.

As has been previously shown,[3] in leading the current from any pair of the three extremities customarily chosen, the three principal peaks, P, R, and T, are usually directed upward in normal subjects. The tall peak R is of especial interest in hypertrophy, and we shall refer to R in lead I as R I, in lead II as R II, etc. Normally all three are directed upward, and of the three, R II is usually of greatest height, R III of least. It has been shown by Einthoven,[4] and confirmed by others, that in hypertrophy of the right ventricle, R I is very small in extent upward, or may be directed downward, usually the latter in well-marked cases; at the same time R III is directed upward, and is relatively of greater magnitude than in normal subjects (Fig. 1). In hypertrophy of the left ventricle, the opposite condition obtains, R I being directed upward, and often of enormous height, while R III is directed downward, frequently to the extent of 2 cm. (or 2 millivolts) (Fig. 2).

As before mentioned the theoretical explanation of these facts is difficult, and in the absence of more definite knowledge, extensive speculation would be unprofitable. The empirically determined facts that a downward directed R I with upward directed R III signifies right ventricular hypertrophy, and that an upward directed R I with downward directed R III means left hypertrophy, are of the greatest clinical significance. While in most cases the ordinary methods of physical examination suffice for a diagnosis of left hypertrophy, the determination of right hypertrophy is not infrequently a matter of much uncertainty, and with thick chest walls, emphysematous lungs, or in the presence of fluid, consolidation, or newgrowths, the difficulty may be unsurmountable.

So far as we know at present, the only conditions, aside from hypertrophy, which can produce a similar electrocardiogram, are changes in position of the heart in the chest and lesions of one limb of the auriculoventricular bundle. It has been found by us that to produce, by change in position of the normal heart, changes comparable to those caused by hypertrophy, requires a very considerable displacement of the organ. As this will form the subject of a subsequent communication, it will not be dealt with in detail here. Such anomalies of position, however, are of comparatively infrequent occurrence as congenital phenomena, and, as a rule, pathological conditions which could cause marked alteration in the position of the heart present little difficulty in diagnosis. We shall have occasion to consider lesions of one limb of the bundle of His a little later.

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[3] James and Williams, The Electrocardiogram in Clinical Medicine, part i, AMER. JOUR. MED. SCI., 1910, cxl, 408.

[4] Le Télécardiogramme, Archiv. internat. de Physiol., 1906, iv, 147; Weiteres über das Elektrokardiogramm, loc. cit., S. 553.

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ORIGINAL ARTICLES.

URIC ACID IN GOUT.[1]

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Introduction. Up to the present time the only chemical problem considered in gout has been that of uric acid. As yet no other chemical standpoint has been found. Are we on the right track in doing this? Is uric acid really the principal toxic agent in gout, or only one of many? From time to time, especially when there appeared to be no progress in the investigation of the subject, protests arose that research was on the wrong path.

The relations between uric acid and the occurrences in gout become evident in the acute periods. The attacks are certainly connected in some way (yet to be determined) with the accumulation of this substance in the body, and during the attacks the

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[1] An address delivered at a meeting of the Harvey Society of New York, April 12, 1910.